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# Cardiac dysfunction *in pauci* symptomatic human immunodeficiency virus patients: a meta-analysis in the highly active antiretroviral therapy era

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**Aims** Human immunodeficiency virus infection (HIV) has been associated with cardiac dysfunction that, if present, can negatively affect morbidity and mortality of HIV-infected patients. Unfortunately, many of the studies on this topic were performed before the highly active antiretroviral therapy (HAART) was established. Thus, we performed a comprehensive meta-analysis to critically appraise the incidence of cardiac dysfunction in HIV-infected pauci symptomatic patients.

**Methods and results** Medline, Cochrane Library, and Biomed Central were systematically screened for studies reporting on systolic and/or diastolic dysfunctions in HIV pauci-symptomatic patients. Baseline treatment and cardiac imaging data were appraised and pooled with random effect methods computing summary. At pooled analysis, including a total of 2242 patients from 11 studies, an overall average incidence of traditional cardiovascular risk factors was observed, while a low rate of previous coronary artery disease was reported. Incidence of systolic and diastolic left ventricular dysfunction was 8.33% (95% CI: 2.20–14.25) and 43.38% (95% CI: 31.73–55.03), respectively. Diastolic dysfunction was graded as first [31.85% (95% CI: 24.85–43.73)], second [8.53% (95% CI: 2.12–14.93)], and third degree [3.02% (95% CI: 1.78–4.27)]. At multivariate analysis, a high sensitivity C-reactive protein level >5 mg/L, active tobacco smoking and previous history of myocardial infarction were predictors of left ventricular systolic dysfunction [odd ratio 1.70 (95% CI: 1.03–2.77); 1.57 (95% CI: 1.03–2.34); and 15.90 (95% CI: 1.94–329.00), respectively]. Hypertension (OR = 2.30; 95% CI: 1.20–4.50) and older age (OR = 2.50 per 10 years increase; 95% CI: 1.70–3.60) were predictors of left ventricular diastolic dysfunction (*Figure 3*).

**Conclusions** Systolic and diastolic dysfunction represent a common finding *in pauci* symptomatic HIV-infected patients, regardless to HAART.

**Keywords** HIV • Heart failure • HAART • Antiretroviral therapy • Echocardiography

## Introduction

Several studies have reported a strong association between human immunodeficiency virus (HIV) infection and cardiac abnormalities, which are closely associated with high morbidity and mortality.[1,2] Human immunodeficiency virus itself, as well as the autoimmune response, and the high cardiovascular risk profile of HIV-positive patients are the main mechanisms leading to cardiac dysfunction.[2]

With regard to coronary heart disease, recent data[3,4] have suggested antiretroviral therapy as a predictor of atherosclerotic plaque progression possibly resulting in consequent ischaemic events.

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The occurrence of cardiomyopathy secondary to HIV infection is less common, but it has been reported in up to 10% of these patients.[5–9] In most of the cases, cardiac dysfunction is transient and asymptomatic; however, progression towards overt left ventricular (LV) failure has been previously described.[9] Unfortunately, many of the studies on this topic were performed before highly active antiretroviral therapy (HAART) became the mainstay of treatment for HIV-positive patients. This combination of drugs resulted in a significant reduction in the incidence of myocarditis and opportunistic infections leading to a drop in Human immunodeficiency virus-associated cardiomyopathy, thus contributing to a greater life expectancy.[10]

However, the real incidence of clinical or subclinical cardiac abnormalities remains uncertain in spite of contemporary cardiac imaging techniques capable of detecting even mild degrees of systolic and diastolic LV dysfunction. Therefore, a meta-analysis was performed in order to critically appraise the real incidence of cardiac dysfunction in HIV-infected pauci-symptomatic population receiving HAART.

# Methods

The present research was elaborated according to current guidelines, including the recent Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) amendment to the Quality of Reporting of Meta-analyses (QUOROM) statement, and recommendations from The Cochrane Collaboration and Meta-analysis Of Observational Studies in Epidemiology (MOOSE).[11–14] No language restrictions were applied.

## Search strategy and study selection

Pertinent articles were searched in Medline, Cochrane Library, Biomed Central in keeping with established methods[15] with MESH strategy and with terms related to HIV patients presenting LV dysfunction: [heart failure OR cardiomyopathy OR ((systolic OR diastolic) dysfunction)] AND [HIV OR aids OR (human AND immunodeficiency AND virus)]. Studies appraising HIV patients cohort alone or both HIV- and non-HIV-positive patients were also included.

Three independent reviewers (G.B.-Z, F.D.A., and E.C.) first screened retrieved citations at the title and/or abstract level, with divergences resolved after consensus. If potentially pertinent, they were appraised as complete reports according to the following explicit selection criteria. Studies were included if (i) investigating systolic or diastolic LV function in HIV patients using a specific cardiac imaging technique [at least one in each study between echocardiography or single photon emission computed tomography (SPECT)] (ii) with clearly description and properly assessment of echocardiography/SPECT data according to current guidelines;[16,17] (iii) with >5% of patients treated with HAART (defined as the use of three or more antiretroviral drugs in combination). Exclusion criteria were (i) non-human setting, (ii) duplicate reporting (in which case the manuscript reporting the largest sample of HIV-positive patients was selected), or (iii) unclear or low prevalence of patients treated with HAART.

## Data extraction

Three unblinded independent reviewers (G.B.-Z, F.DA, and E.C.) abstracted the following data on pre-specified forms: authors, journal, year of publication, location of the study group, baseline features, type and timing of antiretroviral therapy, and NYHA class. Endpoints of interest were rates of systolic or diastolic dysfunction and their clinical or instrumental predictors.

For each study the definition of systolic dysfunction was defined as an ejection fraction (EF) <55% (i) as measured by echocardiography (ii) or as measured by SPECT.

Diastolic dysfunction was defined according to a multiparametric approach (including pulse and tissue Doppler parameters) and graded as mild, moderate, or severe (1, 2, or 3), according to the American Society of Echocardiography guidelines.[16]

Multivariate predictors were appraised if derived from studies with a sample size larger than 100 patients.

## Internal validity and quality appraisal

Unblinded independent reviewers (G.B.-Z., F.D.A., and E.C.) evaluated the overall quality of included studies on pre-specified forms. Modifying the MOOSE items to take into account the specific features of included studies,[14] we separately abstracted and appraised study design, setting, data source, as well as risk of analytical, selection, adjudication, detection, and attrition bias (expressed as low, moderate, or high risk of bias, as well as incomplete reporting leading to inability to ascertain the underlying risk of bias).

## Data analysis and synthesis

Both for continuous and categorical variables, statistical pooling was performed according to a random-effect model with generic inverse-variance weighting, computing risk estimates with 95% confidence intervals, using RevMan 5 (The Cochrane Collaboration, The Nordic Cochrane Centre, and Copenhagen, Denmark). Standard hypothesis testing was set at the two-tailed 0.05 level.

# Results

The systematic literature search yielded 356 citations that were first screened and appraised at the abstract level; 17 articles were then selected, among which 6 were excluded, because including HIV-positive patients not receiving HAART, treated with a single antiretroviral drug or because <75% of included patients were treated with HAART[18–23] (*Figure 1*). Therefore, 11 studies were finally included in our meta-analysis; in 9 of them echocardiography was the imaging technique used for the evaluation of systolic and diastolic function,[24–32] while SPECT was used in others.[33,34]

A total of 2242 patients were included, with a median age of 42 years (95% CI: 39–45) showing at pooled analysis an overall average incidence of traditional cardiovascular risk factors, with a low rate of previous coronary artery disease [2.40% (95% CI: 1.32–6.11)] (*Table 1*).

Human immunodeficiency virus syndrome features are reported in *Table 2*. Cardiac imaging evaluation was performed at a median time of 8.1 (6.3, 10.0; 95% CI) years after HIV-infection diagnosis. Most of the patients were treated with HAART [98.45% (98.14–98.75; 95% CI)] and showed a mild to moderate reduction in CD4 + cell count per $mm^3$ [median 489.33 (356.28, 622.38; 95% CI); Nadir 199.09 (165.81, 232.37; 95% CI)]. Nucleoside reverse-transcriptase inhibitors [75.30% (95% CI: 59.70–90.90)] were the most widely used drugs, followed by non-nucleoside reverse-transcriptase inhibitors [40.43% (95% CI: 28.78–52.08)] and by protease inhibitors [25.42% (95% CI: 10.58–40.26)]. The median overall

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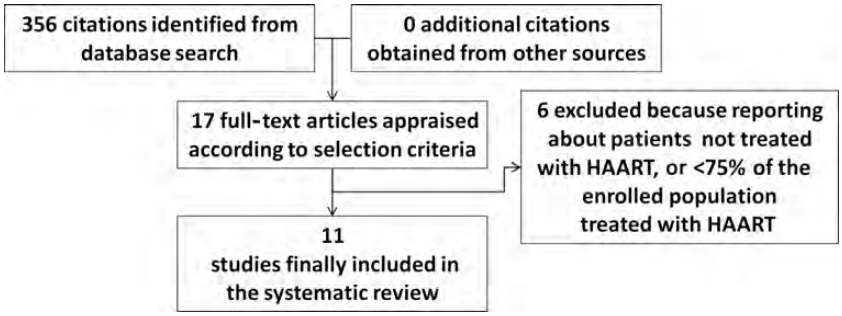


**Figure 1** Review's profile.

**Table 1 Baseline features**

| | Pooled analysis (95% CI)[a] |
|---|---|
| Age (years) | 42.02 (39.19–44.85) |
| Hypertension | 21.09 (15.02–27.16) |
| Patients with hypertriglyceridaemia | 15.79 (7.02–24.56) |
| Diabetes mellitus | 4.81 (2.24–7.37) |
| Current smoker | 23.38 (9.44–37.33) |
| Previous coronary artery disease | 2.40 (1.32–6.11) |
| NYHA | I (I–II) |

[a]Values are median or percentages

**Table 2 HIV syndrome's features**

| | Pooled analysis (95% C.I.)[a] |
|---|---|
| Time from diagnosis of HIV infection (years) | 8.12 (6.26–9.99) |
| Median CD4 + cell count per $mm^3$ | 489.33 (356.28–622.38) |
| Nadir of CD4 + cell count per $mm^3$ | 199.09 (165.81–232.37) |
| Patients with undetectable copies of HIV-RNA in blood | 74.43 (63.71–85.15) |
| Patients treated with highly active antiretroviral therapy | 98.45 (98.14–98.75) |
| Duration of HAART exposure (months) | 56.62 (31.83–81.40) |
| Patients exposed to protease inhibitors (previous or current) | 25.42 (10.58–40.26) |
| Patients exposed to non-nucleoside reverse-transcriptase inhibitors (previous or current) | 40.43 (28.78–52.08) |
| Patients exposed to nucleoside reverse-transcriptase Inhibitors (previous or current) | 75.30 (59.70–90.90) |

[a]Values are median or percentages.

duration of HAART exposure was 56.6 months (31.8–81.4; 95% CI). At the time of cardiac imaging all patients were asymptomatic (NYHA I) without clinical overt signs of heart failure.

At the pooled analysis, the occurrence of systolic and diastolic LV dysfunction was 8.33% (95% CI: 2.20–14.25) and 43.38% (95% CI: 31.73–55.03), respectively (*Table 3*, Supplementary material online, *Figure SA1*). Very similar results were obtained after the exclusion of studies which used SPECT to assess ventricular function [LV systolic dysfunction 10.12% (95% CI: 3.10–17.14)].

When reported, diastolic dysfunction was graded as first [31.85% (95% CI: 24.85–43.73)], second [8.53% (95% CI: 2.12–14.93)], and third degree [3.02% (95% CI: 1.78–4.27)] (Supplementary material online, *Figure SB2*).

At multivariate analysis, a high sensitivity C-reactive protein (sharp) level >5 mg/L, active tobacco smoking and previous history of myocardial infarction were predictors of LV systolic dysfunction [odd ratio = 1.70 (95% CI: 1.03–2.77); 1.57 (95% CI: 1.03–2.34); and 15.90 (95% CI: 1.94–329.00), respectively] (*Figure 2*).

Hypertension (OR = 2.30; 95% CI: 1.20–4.50) and older age (OR = 2.50 per 10 years increase; 95% CI: 1.70–3.60) were predictors of LV diastolic dysfunction (*Figure 3*).

The methodological assessment (Supplementary material online, *Tables SA1* and *SB2*) showed an overall good quality of the selected studies, most of them being prospective, one-third of them multicenter, without high risk of analysed bias (Supplementary material online, *Figure SC3*). The vast majority of the included studies was performed in Europe or North America.

## Discussion

The present systematic review and meta-analysis summarizes the available evidence regarding the incidence of cardiac dysfunction in HIV-positive pauci-symptomatic patients. Several studies, performed before the current HAART era, have identified cardiac abnormalities in HIV patients. In particular, the incidence of LV systolic dysfunction ranged from 10 to 40% depending on the progression of the disease, on the type of definition used for 'systolic impairment' and on the presence of a concomitant drug abuse;[35–37] however, clinically symptomatic cardiomyopathy has been reported in up to 10% of HIV-positive patients only.[5,6] In two studies a very high incidence of LV diastolic dysfunction has also been reported.[38,39]

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**Table 3 Details regarding left ventricular function assessment**

| | |
|---|---|
| Studies performed with | $n = 11$ |
| Ecocardiography | 9 (80) |
| SPECT | 2 (20) |
| Echocardiographist | |
| Blinded to patients' disease | 8 (88) |
| Unclear | 1 (12) |
| Number of echocardiographists | |
| 1 | 3 (33) |
| 2 | 4 (44) |
| 3 | 1 (11) |
| Unclear | 1 (11) |
| Definition of diastolic dysfunction | $n = 7$ |
| Spectral Doppler mitral and pulmonary venous inflow velocity patterns and Doppler tissue imaging of the lateral mitral annulus. Using the average of septal and lateral early diastolic velocities (Ea), the E/Ea ratio was computed. Three cardiac cycles were measured and averaged for all Doppler measurements | 7 (100) |
| Definition of systolic dysfunction | $n = 11$ |
| Left ventricular (LV) dysfunction was defined as an ejection fraction <50% | 8 (73) |
| Left ventricular (LV) dysfunction was defined as an ejection fraction <55% | 1 (9) |
| LVEF was measured using a multiple electrocardiogram-gated equilibrium study in which the gamma camera was positioned in a left anterior oblique 301 view, with a caudal tilt of 51–101, and adjusted for optimal separation of the ventricles | 2 (18) |

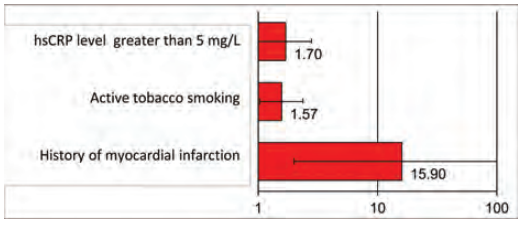


**Figure 2** Multivariate predictors of systolic dysfunction (reported as OR; 95% CI).

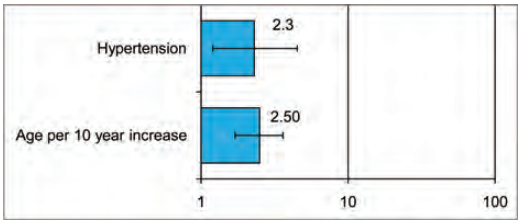


**Figure 3** Multivariate predictors of diastolic dysfunction (reported as OR; 95% CI).

Different potentially contributing factors cause HIV-related cardiomyopathy. Viral, toxoplasmatic or fungal opportunistic infections and nutritional deficiencies (e.g. selenium) may play an important role.[40,41] It has also been hypothesized a direct invasion of the HIV genome in the cardiomyocytes or an autoimmune response triggered by the restoration of the immune competence during antiretroviral therapy.[42–44] All the mechanisms mentioned above are related to severe immunodeficiency combined with a high viral load. As reported by Twagirumukiza *et al.*[45] in a multicenter, observational, prospective, cohort study of 416 not-HAART-treated patients, duration of HIV-1 infection, CD4 count, and HIV-1 viral load were associated with the development of cardiomyopathy both at univariate and multivariate analysis.

The introduction of HAART represented a turning point also for the cardiac involvement of HIV patients, with a nearly 30% reduction in HIV-associated cardiomyopathy.[10] However, our meta-analysis shows that both systolic and/or diastolic dysfunction persist despite a fully active antiretroviral treatment (leading to a mild or moderate reduction in CD4 cell count) and despite the suppression of viral replication below the detection limit in three out of four patients. The duration of viral suppression and the threshold level to be reached in order to achieve a reduced risk of HIV-associated disorders are currently not known. Several factors may probably play a role in the development of the disease: for example, an impact of antiretroviral drugs has not been well defined. The influence of antiretroviral drugs on cardiovascular system is still a matter of debate and a fully-accurate single-drug effect analysis remains challenging. Anyway, at multivariate adjustment, HAART drugs did not significantly relate either to systolic or diastolic dysfunction.

The impact of cardiac dysfunctions on prognosis has not been well analysed. In a pre-HAART study of 70 HIV asymptomatic patients,[46] LV systolic dysfunction (defined as EF <45% and fractional shortening <28%) was reported in 11% of them. Most of the abnormalities were transient and not consistently associated with a clinical progression of the disease. Conversely, a persistently low LV EF was associated with a high mortality rate within the first year of the follow-up. Therefore, further follow-up data are necessary to confirm these findings even in the HAART therapy era and additional studies are needed to evaluate the impact of these dysfunctions on survival and quality of life to better define if these patients require a closer follow-up and to test the potential benefit of drugs commonly used for heart failure treatment (e.g. ACE inhibitors, beta-blockers, and mineral corticoid receptor antagonists).

In addition to imaging parameters, also elevated levels of hsCPR were independent predictors of systolic dysfunction. In previous studies, high sensitivity C-reactive protein levels have been shown to be elevated in patients with HIV compared with healthy subjects[47] and increased high sensitivity C-reactive protein levels were also associated with a higher relative risk of acute myocardial infarction.[48,49] The relationship between high

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sensitivity C-reactive protein levels and the risk of cardiac dysfunction in HIV patients has also been previously described highlighting the role of inflammation, partly triggered by HIV virions and their harmful effect on cardiomyocytes, partly by the local release of cytokines.[50] Our findings could reflect the presence or the consequence of a myocarditic process in the immunodeficient setting of a HIV-positive population.[51,52] Thus, some studies support the role of serologic testing and of C-reactive protein as a marker of persistent viral infection and development of dilated cardiomyopathy.[53,54] Cardiac magnetic resonance imaging could be helpful in identifying and characterizing myocardial abnormalities, explaining in which proportion cardiac dysfunctions arise from HIV infection itself. Anyway, the clinical impact of C-reactive protein elevation remains to be defined because it may reflect both the status of the disease, both an epiphenomenon of HIV infection, even if the study from which was derived (Mondy *et al.*[32]) enrolled only patient receiving routine outpatient care.

Our work shares several important limitations. First, we appraised infrequent events, with all the limits of reporting uncommon outcomes.[55] Secondly, no specific data about the influence of different associations of antiretroviral drugs were available, making a pooled analysis unfeasible. Thirdly, it was not possible to analyse data about baseline treatment and compliance and, as a consequence, to address their role and influence in controlling cardiovascular risk factors and inflammation level. Also, data regarding illicit drugs used were not consistently reported in the included studies as well as data about concomitant infections (e.g. myocarditis), therefore their impact on LV dysfunction was impossible to gauge. However, it should be taken into account that both illicit drug abuse and infections have become infrequent in the current HAART era.[39] Finally, as in all studies based on cardiac imaging, intra- and inter-observer variability may have limited the accuracy of LV function estimation and the reliability of our analysis.

In conclusion, the occurrence of systolic and/or diastolic dysfunction in HIV-positive patients receiving HAART is a common, possibly underecognized, finding, regardless to HAART.

**Conflict of interest:** none declared.

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